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RESEARCH ARTICLE

The preparation of α-aminopropane phosphonic acid via the catalyzed hydrogenation of dimethyl or diethyl α-hydroxyiminopropanephosphonate

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Abstract

The use of catalytic hydrogenation for the conversion of α-hydroxyiminophosphonates into α-aminophosphonates (and hence α-aminophosphonic acids) is reviewed. Using the synthesis of α-aminopropanephosphonic acid as a specific example for study, the effects of variation in reaction conditions have been investigated. It has been found that both Raney nickel and palladium on activated carbon are effective catalysts at elevated temperatures and pressures, but that traces of nickel may contaminate the finally isolated aminophosphonic acid if Raney nickel is used. The formation of an aminophosphonate-nickel complex is a possible complication. Yields were found to fall as the reactant concentration was increased although this effect was offset by carrying out the hydrogenation in the presence of liquid ammonia. Optimum yields were in the region of 60-65%.

Keywords

Hydroxyiminophosphonate · aminophosphonate · aminophosphonic acid · catalytic hydrogenation · nickel · palladium

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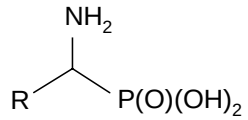
1 Introduction

$\alpha-$Aminophosphonic acids (**1**) are analogues of the naturally occurring α-amino-carboxylic acids (**2**) and are important biologically active compounds, either as the free acids or as peptide derivatives [1].



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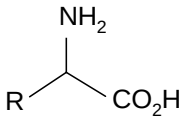

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Numerous methods for their preparation have been reported and have been reviewed comprehensively elsewhere [2]. We now report our experience with one such method based on the use of acylphosphonates (**3**), their conversion into the corresponding oximes (**4**), and then reduction to the aminophosphonates (**5**) (Fig. 1). The aminophosphonic acids (**1**) can then be obtained by hydrolysis, using aqueous hydrochloric acid, followed by suitable adjustment of the pH to liberate the free acids from their hydrochloride salts. The simplest procedure for the removal of HCl is by crystallization from methanol/propylene oxide [3].

Acylphosphonates (**3**) (otherwise known as α-oxo- or α-ketophosphonates) can easily be obtained in high yield by the interaction of trialkyl phosphites with acyl chlorides [4] and the possibility of their direct conversion into α-aminophosphonates (**5**) by reductive amination, as reported [5] for the analogous β-keto-derivatives (**6** and **7,** Fig. 2), is therefore attractive.

However, α-ketophosphonates (**3**) are susceptible to P-C cleavage by nucleophilic reagents [6], including ammonia (Fig.3) and their direct conversion into the α-amino compounds by reduction in the presence of ammonia is not feasible.

Nevertheless, it has been reported that the free α-ketophosphonic acids (**3**, R' = H) (but not the mono or di-esters) can be converted successfully into the corresponding aminophosphonic acids in 50 – 70% yield, using sodium borohydride in the presence of aqueous ammonia or an amine [7, 8]. This procedure does, however, require the prior preparation of the dibenzyl esters which are subjected to debenzylation by

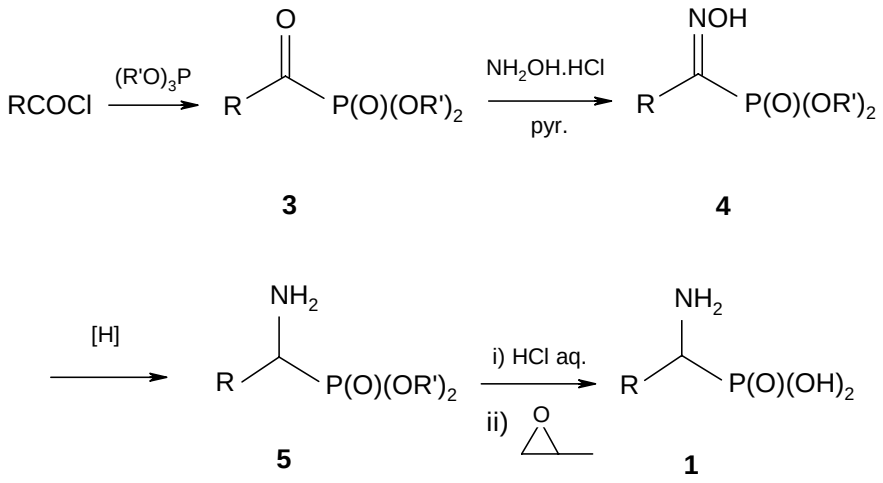


Fig. 1.

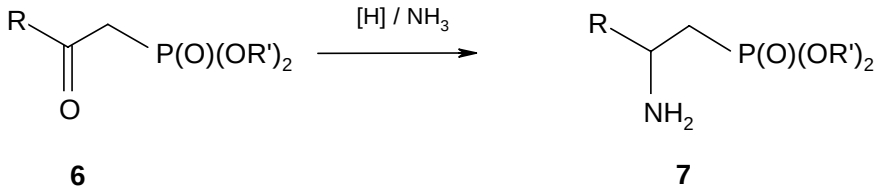


Fig. 2.

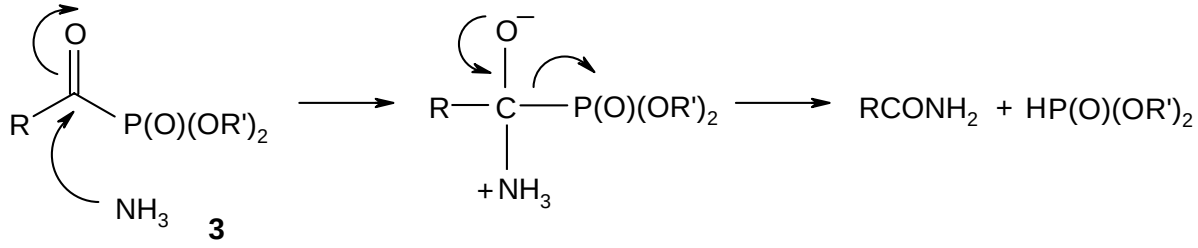
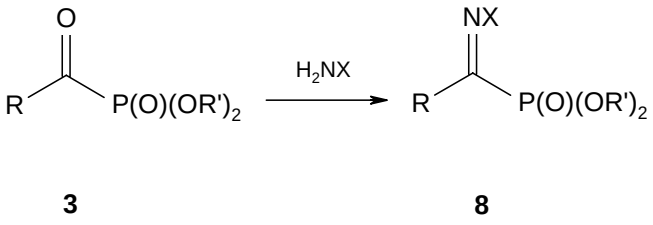


Fig. 3.

hydrogenolysis in the presence of palladium.

The conversion of dialkyl α-ketophosphonates into α-aminophosphonates generally involves the intermediate formation of a suitable imino derivative (**8,** Fig 4), the first reported example being the *p*-nitrophenylhydrazone of diethyl benzoylphosphonate (**8a**, R = Ph. R' = Et) which was reduced by aluminium amalgam to give diethyl α-aminobenzylphosphonate (**5**, R = Ph, R' = Et) [9]. Numerous similar procedures have been described, involving the reduction of phenyl- and dimethylhydrazones (**8b,c**) [10], oximes (**8d**) [11], and *O*-substituted oximes (**8e**) [12]. Oximes have been most commonly used, and the reduction has been carried out with a wide variety of reagents [2,13], including aluminium amalgam [11], activated zinc in formic acid [14], sodium borohydride [12], diborane in THF [15], zinc-copper couple in aqueous ethanol [16], lithium borohydride/trimethylsilyl chloride [17,18], and sodium triacetoxyborohydride/titanium trichloride [19].

A more attractive possibility on the technical scale, which would avoid the use of expensive chemical reducing agents and/or lengthy work-up procedures, is catalytic hydrogenation of the α-hydroxyiminophosphonate (**8d**), although there are surprisingly few references to this approach in the literature.



X = $NHC_6H_4NO_2$-*p* (a); NHPh (b); NMe_2 (c); OH (d); OR'' (e)

Fig. 4.

The first report on the use of hydrogenation in the presence of Raney nickel [20] described the conversion at 100 ^oC and 80 Kg m^2 pressure, of a number of diethyl α-hydroxyiminophosphonates (**4**, R = Et, Me_2CH, Me_2CHCH_2, EtMeCH, Ph, $PhCH_2$; R' = Et) into the corresponding α-aminoalkanephosphonate esters (**5**). A surprisingly short reaction time was reported (10 min) and the solvent, if any, was not mentioned. The crude diethyl α-aminophosphonates (**5**) were characterized as the *N*-benzoyl derivatives and were also hy-

drolyzed by heating under reflux with concentrated hydrochloric acid (48 h) to give the corresponding acids (**1**), isolated either as the hydrochlorides (R = Et, or Ph) or as the free acids, after recrystallization from aqueous methanol. (Propylene oxide was not used to remove HCl, as described elsewhere [3]). Yields overall, based on the acylphosphonates (**3**), were low (in the range 7 – 40%).

The use of Raney nickel in ethanol at 100 ^{o}C and 80 atm pressure, with a much longer reaction time of 12 hours, was subsequently reported [21] for the preparation of a series of diethyl 1-amino-2-arylethylphosphonates [**5**, R = 4-EtC_6H_4, 2-, 3-, and 4-MeOC_6H_4, 4-EtOC_6H_4, 4-Bu^nOC_6H_4, 2,3-$OCF_2OC_6H_3$, 4-PhOC_6H_4, 4-(4'-ClC_6H_4O)C_6H_4, and 4-(4'-FC_6H_4O)C_6H_4]. The distilled products were hydrolysed by heating under reflux with 20% hydrochloric acid to give the corresponding 1-amino-2-arylethylphosphonic acids (**1**), which were crystallized from methanol-propylene oxide. Yields for each stage of this process were mainly in the range 60 - 90%. Results were also given for a number of similar products having additional substituents at the α-carbon atom and for some related heterocyclyl derivatives. Hydrogenation in solvents other than ethanol (e.g. THF or dioxan) was found to be unsatisfactory and led to no isolable products [21]. The only other reference to the Raney nickel-catalyzed hydrogenation of an α-hydroxyiminophosphonate [22] referred specifically to the preparation of the diethyl ester of the phosphonic analogue of tryptophan (**5**, R = indol-3-yl-CH_2, R' = Et), which was isolated as the oxalate in 75% yield. The hydrogenation was carried out in anhydrous ethanol at 100 ^{o}C/100-120 atm (1 h). The use of palladium for the catalytic hydrogenation of α-hydroxyiminophosphonates does not appear to have been reported, although rhodium on alumina has been used in one instance (**4**, R = Ph, R'=Et) [21].

In this paper we report our studies on the catalytic hydrogenation of dimethyl and diethyl α-hydroxyiminopropanephosphonate in the synthesis of α-aminopropanephosphonic acid (**1**, R = Et), a compound which was of interest to us because of its potential as a low toxicity seed-dressing for the control of certain diseases of cereal crops [23-25].

2 Results and discussion

2.1 Preparation and oximation of the acylphosphonate (α-oxo- or α-keto-phosphonate).

The Arbuzov reaction between a triakyl phosphite and acyl chloride occurs readily to give the corresponding acylphosphonate (**3**) in high yield [4]. The standard method for the preparation of the oxime (**4**) employs hydroxylamine hydrochloride in the presence of pyridine [11,20] and we have found this method to be the most satisfactory.

Separation from the pyridine hydrochloride by-product, and excess pyridine if present, was carried out as described [11] by acidification with hydrochloric acid and extraction of the oxime with dichloromethane. Purification of the oxime by distillation is not feasible as it is heat sensitive [26] but the product obtained as described is sufficiently pure for direct use in the next stage of the synthesis. The use of hydrochloric acid in the work-up procedure appears to favour isomerization of the *Z*-isomer to the *E*-isomer [27], which was the only isomer detectable by ^{31}P nmr in the final product.

2.2 Hydrogenation of the α-hydroxyiminophosphonates

At room temperature and 2.5 atm pressure palladium failed to catalyze the hydrogenation either in acetic acid or anhydrous ethanol. Raney nickel also failed at room temperature and 20 atm, but at the same pressure and 100 ^{o}C the oximes were reduced. Hydrolysis of the so-formed dialkyl aminophosphonate esters (R' = Me or Et), by heating under reflux with hydrochloric acid in acetic acid, then gave α-aminopropanephosphonic acid (**1**, R = Et) in an overall yield of 60-65%.

A significant problem encountered when using Raney nickel was that the intermediate dialkyl α-aminophosphonates were contaminated with a substantial amount of dissolved nickel. Consequently, the ^{1}H NMR spectra of these products consisted of ambiguous broad peaks which were of no use for characterization. The α-aminopropanephosphonic acid obtained by hydrolysis of dimethyl α-aminopropanephosphonate was also seen to have a light green colour and was shown by atomic absorption spectroscopy to contain *ca.* 0.33% Ni. Further crops of the acid obtained from the mother liquors remaining from recrystallization were shown to contain 11.2% nickel, suggesting that a 3:1 aminophosphonic acid-nickel complex might have been formed. Analogous 3:1 metal complexes have been reported for divalent metal cations, including Ni(II), with amino-carboxylic acids [28]. Ion-exchange chromatography would be necessary for complete separation of the aminophosphonic acid.

When the oxime reduction was carried out at higher reactant concentrations, the yield of aminophosphonic acid obtained fell. Thus, as the initial oxime concentration was increased from 2 to 7, and then to 21% w/v (entries 4-6, Table 1), the yield of aminophosphonic acid fell from 65 to 41, and 27%, respectively. This loss in yield might be due to intermolecular interactions between molecules of the dialkyl aminophosphonate (which we have found to be liable to polymerization on distillation [17]), or the formation of secondary amines – a known type of reaction in various types of hydrogenation process [29]. To suppress the latter possibility, liquid ammonia was added to the reaction mixture, thereby increasing the yield of aminophosphonic acid isolated to 52%, when working with an initial oxime concentration of 15% (entry 8, Table 1). Excess ammonia was removed before hydrolysis of the aminophosphonate ester by repeated evaporation in the presence of added water, in order to avoid contamination of the product with large amounts of ammonium chloride which would be difficult to separate from the water-soluble product.

The best overall yield was obtained with 5% palladium on car-

bon at 115 ^{o}C, at a pressure of 27 atm, and in the presence of ammonia. Under these conditions, and with an initial oxime concentration of 33% (entry 9), α-aminopropanephosphonic acid (**1**, R = Et) was isolated in 61% yield in a high state of purity and with no contamination from residual catalyst. There is no doubt scope for further optimization of the reaction conditions and for the development of procedures for the recycling of ammonia and the solvent (methanol or ethanol).

For the catalytic hydrogenation of α-hydroxyiminophosphonates in general, the most suitable conditions can be expected to vary according to the structure and properties of the particular hydroxyiminophosphonate in question and will be dependent on such factors as thermal stability, reactivity towards alcoholic or other solvents [30], and the possibilities of polymerization resulting from interaction between product molecules [17].

3 Experimental

3.1 Starting materials

Trimethyl phosphite, triethyl phosphite, hydroxylamine hydrochloride, pyridine, and other general reagents and solvents were obtained commercially and used as supplied. Propionyl chloride was redistilled before use. Raney nickel (ex Aldrich) was washed free of alkali by repeated decantation of added water, and then finally with ethanol/ether to give a slurry which was added to the reactor. Palladium (5%) on activated carbon was supplied by Aldrich.

3.2 Instrumentation

NMR spectra were recorded on a Bruker WP-80 FT spectrometer operating at 80.02 MHz, 20.12 MHz, and 32.395 MHz for ^{1}H, ^{13}C, and ^{31}P spectra, respectively. Chemical shifts (downfield positive) are given relative to TMS (in $CDCl_3$) or 3-trimethylsilylpropionate (in D_2O) for ^{1}H and ^{13}C spectra, and 85% phosphoric acid (external standard) for ^{31}P spectra. Infrared spectra were run as liquid films on Pye Unicam SP2000 and SP3-200 spectrophotometers. Analysis for nickel was carried out on a Pye Unicam Atomic Absorption Spectrophotometer, model SP9.

3.3 Preparation of dimethyl propionylphosphonate [31]

Propionyl chloride (323 g, 3.49 mol) was added dropwise to trimethyl phosphite (383 g, 3.08 mol) under nitrogen with stirring at 25 ^{o}C, the temperature being controlled by cooling in an ice bath. The mixture was stirred at room temperature overnight and then distilled to give dimethyl propionylphosphonate (446 g, 2.69 mol, 87%) as a clear liquid, b.p. 89-90 ^{o}C at 3.5-4.0 mmHg (lit. [31] 60-62 ^{o}C at 1 mmHg), ν_{max}/cm^{-1} (film) 1040 (P-O-C), 1265 (P=O), 1695 (C=O); δ_H ($CDCl_3$) 1.12 (3H, t, C$\underline{H}_3$CH$_2$, $^{3}J_{HCCH}$ 7.10 Hz), 2.88 (2H, q, CH$_2$, 7.10 Hz), 3.89 (6H, d, CH$_3$O, $^{3}J_{POCH}$ 10.74 Hz); δ_C ($CDCl_3$) 6.4 (d, $\underline{C}$H$_3$CH$_2$, $^{3}J_{PC}$ 4.3Hz), 37.2 (d, CH$_2$, $^{2}J_{PC}$ 56.8 Hz), 54.0 (d, CH$_3$O, $^{2}J_{POC}$ 7.3 Hz), 211.0 (d, C=O, $^{1}J_{PC}$ 166.0 Hz); δ_P ($CDCl_3$) –1.1.

3.4 Preparation of diethyl propionyl-phosphonate [32]

Similarly, propionyl chloride (9.62 g, 0.104 mol) and triethyl phosphite (17.3 g, 0.104 mol) gave diethyl propionylphosphonate (12.1 g, 0.62 mol, 60%), b.p. 74-78 ^{o}C at 1.0 mmHg (lit. [32] 105 ^{o}C at 7 mmHg), ν_{max}/cm^{-1} (film) 1020 (P-O-C), 1265 (P=O), 1695 (C=O); δ_H ($CDCl_3$) 1.04 (3H, t, C$\underline{H}_3$CH$_2$CH$_2$, $^{3}J_{HCCH}$ 7.10 Hz), 1.35 (6H, t, C$\underline{H}_3$CH$_2$O, $^{3}J_{HCCH}$ 7.50 Hz), 2.88 (2H, q, CH$_2$C(O), $^{3}J_{HCCH}$ 7.08 Hz), 4.16 (4H, q, OCH$_2$, $^{3}J_{HCCH}$ 7.00 Hz); δ_C ($CDCl_3$) 6.4 (d, $\underline{C}$H$_3$CH$_2$CH$_2$, $^{3}J_{PCCC}$ 3.7 Hz), 16.4 (d, $\underline{C}$H$_3$CH$_2$O, $^{3}J_{POCC}$ 3.7 Hz), 36.9 (d, $\underline{C}$H$_2$C(O), $^{2}J_{PCC}$ 56.2 Hz), 63.8 (d, OCH$_2$, $^{2}J_{POC}$ 7.3 Hz), 211.5 (d, C(O), $^{1}J_{PC}$ 166.6 Hz); δ_P ($CDCl_3$) –2.9.

3.5 Preparation of dimethylα-hydroxyiminopropanephosphonate [20]

Dimethyl propionylphosphonate (171 g, 1.03 mol) was added dropwise to a mixture of hydroxylamine hydrochloride (82.4 g, 1.19 mol) and pyridine (100 g, 1.26 mol) in methanol (250 cm^{-3}) whilst keeping the reaction mixture below 10 ^{o}C. The mixture was stirred overnight at room temperature and then evaporated under reduced pressure at 40 ^{o}C. Hydrochloric acid (10%, 100 cm^{-3}) was added until pH 2 was reached and the mixture was extracted exhaustively with dichloromethane. The extract was washed with sodium bicarbonate solution (10%, 20 cm^{-3}), dried ($MgSO_4$), and evaporated under reduced pressure at room temperature to give dimethyl α-hydroxyiminopropanephosphonate (163 g, 0.90 mol, 87%) as a waxy low melting solid, ν_{max}/cm^{-1} (film) 1040 (P-O-C), 1240 (P=O), 3190 (OH); δ_H ($CDCl_3$) 1.14 (3H, t, C$\underline{H}_3$CH$_2$, $^{3}J_{HCCH}$ 7.32 Hz), 2.54 (2H, q, C$\underline{H}_2$, $^{3}J_{HCCH}$ 7.32 Hz), 3.80 (6H, CH$_3$O, $^{3}J_{POCH}$ 11.23 Hz), 10.95 (1H, br s, OH); δ_C ($CDCl_3$) 10.2 (s, $\underline{C}$H$_3$CH$_2$), 19.9 (d, $\underline{C}$H$_2$, $^{2}J_{PCC}$ 16.5 Hz), 53.5 (d, CH$_3$O, $^{2}J_{POC}$ 6.1 Hz), 154.7 (d, C=N, $^{1}J_{PC}$ 213.0 Hz); δ_P ($CDCl_3$) 13.6.

3.6 Preparation of diethylα-hydroxyiminopropanephosphonate [20]

Similarly, diethyl propionylphosphonate (28.0 g, 0.144 mol), hydroxylamine hydrochloride (12.4 g, 0.190 mol) and pyridine (16.0 g, 0.202 mol) in dry ethanol (41 cm^{-3}), gave diethylαhydroxyiminopropanephosphonate as a colourless oil (25.2g, 0.120 mol, 84%), ν_{max}/cm^{-1} (film) 1020 (P-O-C), 1230 (P=O), 3190 (OH); δ_H ($CDCl_3$) 1.15 (3H, t, C$\underline{H}_3$, $^{3}J_{HCCH}$ 7.81 Hz), 1.34 (6H, t, C$\underline{H}_3$CH$_2$O, $^{3}J_{HCCH}$ 7.08 Hz), 2.54 (2H, q, C$\underline{H}_2$C(NOH), $^{3}J_{HCCH}$ 7.08 Hz), 4.17 (4H, q, CH$_2$O, $^{3}J_{HCCH}$ 7.57 Hz), 10.87 (1H, br s, OH); δ_C ($CDCl_3$) 10.3 (s, CH$_3$), 16.3 (d, $\underline{C}$H$_3$CH$_2$O, $^{3}J_{POCC}$ 6.1 Hz), 20.0 (d, $\underline{C}$H$_2$C(NOH), $^{2}J_{PCC}$ 16.5 Hz), 63.0 (d, CH$_2$O, $^{2}J_{POC}$ 7.3 Hz), 155.3 (d, C(NOH), $^{1}J_{PC}$ 212.4 Hz); δ_P ($CDCl_3$) 11.0.

Tab. 1. Hydrogenation of α-hydroxyiminopropanephosphonates (**4**, R = Et, R' = Me or Et)

Exp.	R'	Wt/g	Catalyst/g or cm^3		Solvent/cm^3		NH_3 cm^3	Press. atm [a]	Temp. ^oC	Time h	Yield [b] %
1.	Et	1.10	Pd	1.0	AcOH	75	-	2.5	20	3	0
2.	Et	1.00	Pd	0.2	EtOH	20	-	2.5	20	3	0
3.	Et	5.00	Ni	4	EtOH	150	-	20	100	3	60
4.	Me	2.00	Ni	2	MeOH	100	-	20	100	3	65 [c]
5.	Me	6.90	Ni	2	MeOH	100	-	23	100	3	41
6.	Me	18.5	Ni	5	MeOH	90	-	20	100	3	27
7.	Me	6.90	Ni	2	MeOH	100	30	27	100	3	51
8.	Me	20.0	Ni	5	MeOH	100	30	27	100	3	52
9.	Me	21.0	Pd	7.4	MeOH	42	21	27	115	3	61 [d]

[a] Initial pressure in sealed autoclave before heating. [b] α-Aminopropanephosphonic acid (**1**, R = Et) crystallized from methanol by treatment with propylene oxide. [c] m.p. 252-254 ^oC; recrystallization from aqueous methanol gave α-aminopropanephosphonic acid (93% recovery), m.p. 262-264 ^oC (lit. [33]m.p. 264-266 ^oC), δ_H ($CDCl_3$) 1.05 (3H, t, CH_3. $^3J_{HCCH}$ 7.0 Hz), 1.45-2.15 (2H, br m, CH_2), 2.85-3.45 (1H, br, m, CH), with a very light green coloration (Found: Ni, 0.33%). Further crops of crystals obtained from the mother liquor contained 11.2% Ni (calcd. for 3:1 aminophosphonic acid-nickel complex: 12.4%). [d] White crystals, m.p. 262-264 ^oC, δ_H ($CDCl_3$) 1.05 (3H, t, CH_3. $^3J_{HCCH}$ 7.0 Hz), 1.50-2.20 (2H, br m, CH_2), 2.80-3.50 (1H, br m, CH).

3.7 Hydrogenation of dialkylα-hydroxyiminopropanephosphonates

The hydroxyiminophosphonate was dissolved in the specified solvent (Table 1) in the presence of either Raney nickel or 5% palladium on carbon. Hydrogenation was carried out at room temperature (in glass) or at elevated temperature and pressure in a Parr stainless steel 600 ml minireactor (model 4563). In specified cases, liquid ammonia was added prior to hydrogenation (Table 1). The residual catalyst was filtered off and washed with water (after reaction in acetic acid) or with the corresponding alcohol after hydrogenation in methanol or ethanol. The filtrate and washings were combined and evaporated under reduced pressure. The products from reaction in acetic acid were neutralized with aqueous sodium carbonate, extracted with dichloromethane, dried ($MgSO_4$), and evaporated under reduced pressure to leave a residual oil, shown to be the unreacted diethyl α-hydroxyiminopropanephosphonate, δ_H ($CDCl_3$) 1.15 (3H, t, $C\underline{H}_3$, $^3J_{HCCH}$ 7.8 Hz), 1.35 (6H, t, $C\underline{H}_3CH_2O$, $^3J_{HCCH}$ 7.1 Hz), 2.55 (2H, q, $C\underline{H}_2C(NOH)$, $^3J_{HCCH}$ 7.1 Hz), 4.20 (4H, q, CH_2O, $^3J_{HCCH}$ 7.5 Hz), 10.90 (1H, br s, OH).

Products from reaction in methanol or ethanol were, after concentration, heated under reflux with a mixture (1:3 v/v) of glacial acetic acid and concentrated hydrochloric acid for 6 – 8 h. After further evaporation under reduced pressure, the residues were dissolved in warm methanol and treated with propylene oxide [3] to give a white crystalline precipitate, which was filtered off, washed with methanol, and dried in a vacuum oven at 60 ^oC, to give α-aminopropanephosphonic acid (see Table 1).

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